REMARKS

I. Status of the Claims

Claims 1, 11, 19, 22 and 24-27 are pending in the application. Claims 11 and 26 stand withdrawn from consideration as drawn to a non-elected invention. Claims 1, 19 and 22 stand rejected, and claims 24, 25 and 27 stand newly rejected under 35 U.S.C. §112, first paragraph as lacking written description, and claims 1, 19 and 22 stand rejected, and claims 24, 25 and 27 stand newly rejected, also under §112, first paragraph, as lacking enablement. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Written Description

In response to the previous rejection, applicants amended the claims to recite "conservatively modified variants." The examiner has maintained the rejection of the claims, arguing that just as with the term "derivatives," the specification fails to provide teachings sufficient to demonstrate that the inventors were in possession of this subject matter at the time of filing. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to remove any reference to "derivatives" or "variants." Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Enablement

All claims stand rejected as lacking enablement for clinical embodiments. The examiner argues that any evidence presented by the inventors regarding ferritin-H expressed intracellularly is irrelevant to the elected species, which relies on provision of ferritin-H protein, not a nucleic

acid. Moreover, it is argued that to the extent that the inventors have shown *ex vivo* results, these are ineffective to support purely *in vivo* applications. Applicants traverse.

A. Evidence of Intracellular Expression Is Relevant to Enablement

The examiner has dismissed, out of hand, the evidence of record regarding the expression of ferritin-H using genetic transformation. This not appropriate. The first question that one must ask is whether providing ferritin-H ***in any form*** will impact β-globin production. As shown in Example 1, transient expression assays show that increasing ferritin-H expression in cells reduces transcription from the β-globin promoter. Thus, there can be no challenge to applicants' assertion that a method for increasing ferrtin-H levels will result in reduced β-globin expression. This fact, in and of itself, is highly relevant to enablement, and the examiner's total dismissal of the data is inappropriate.

Additional data from the inventors' laboratory provides further credence to their claims that ferritin-H can be used as a therapeutic agent to treat sickle cell anemia. First, the ability of ferritin-H to selectively bind to the β-globin promoter, as contrasted to other ferritins, has been further demonstrated in *in vitro* assays. Second, even a proteolytically generated fragment of ferritin-H can bind effectively to the β-globin promoter *in vitro*. And third, transient expression of a GFP-labeled ferritin-H localizes in the nucleoplasm of cells. Again, though not specifically providing evidence on protein administration, these data are at least ***relevant*** to the issue of whether ferritin-H can impact the phenotype of cells in which ferritin-H can be targeted to the nucleus.

In sum, the data of record, though *in vitro* in nature, provide a strong indication that ferritin-H can act to alter the expression of β-globin genes. Thus, a proper enablement analysis should consider such data and their relevance to the claimed invention.

B. Differences Between Ex Vivo and In Vivo Claims

The examiner and applicant agree that there a differences between *ex vivo* and *in vivo* aspects of the invention. As an initial point, however, applicants note that claim 25 is limited to *ex vivo* embodiments, and thus any arguments regarding the additional difficulties of *in vivo* therapies are not applicable against this claim. Moreover, the examiner's statement that "the understanding to [*sic*] beta globin gene has not translated to clinically effective therapeutic strategy" evinces a standard for enablement that is not proper. Indeed, applicants need not demonstrate a clinically effective therapeutic strategy to support enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Thus, the examiner is posing an incorrect question – has clinical benefit been achieved – when examining enablement.

Moreover, the examiner has offered no explanation as to why, assuming that one could achieve increased levels in the nuclei of ferritin-H in globin-producing cells, those of skill in the art would not expect to achieve a clinical benefit. At most, the examiner has raised potential problems with nuclear targeting, but has provided no ***evidence*** on this point. The burden remains on the examiner to explain why this is would be the case, and in the absence of such evidence, the specification is presumed to be enabling. *In re Marzocchi* 169 USPQ 370 (CCPA 1971).

C. The Only Remaining Question is One of Protein Delivery

As discussed, applicants have shown in a variety of ways that increasing ferrtin-H levels in cell nuclei reduces β globin transcription. Thus, the only relevant question, given the elected species, is whether the instant specification provides an enabling disclosure for increasing ferrtin-H in cell nuclei *ex vivo* and *in vivo* by providing ferritin-H protein. If that question is answered in the affirmative, there is no reason to suspect that a clinical benefit can be achieved using this embodiment.

Attached to this response are three publications from refereed journals that indicate ferritin, when applied exogenously to cells with the appropriate receptors, can be internalized and taken up into cell nuclei. Thus, there is no reason to believe that ferritin-H, when delivered to the appropriate tissue, cannot reach cell nuclei and impact expression of β-globin, either *ex vivo* or *in vivo*.

Meyron-Holtz *et al.* (1999) used human erythroid precursors grown in culture, which are know to possess receptors to isoferritin. ^{59}Fe-labeled isoferritin was shown to transfer label into cells where it was incorporated into hemoglobin. Similarly, Leimberg *et al.* (2003) showed that human erythroid cells utilized extracellular ferritin as an intracellular source of iron for heme synthesis, thereby confirming the ability of cells to take up ferritin.

Thus, it is submitted that the cited art clearly demonstrates that exogenous ferritin can not only be taken up by appropriate cells, but transferred to the nucleus of those cells where it has already been demonstrated to down-regulate expression of β-globin. Thus, this concern of the examiner also has been adequately addressed.

D. Expert Declarations

In addition to the evidence already submitted, applicants now provide the declarations of Dr. John McDonald and Dr. Xinli Lin. The declarants both state that they are familiar with the work of Dr. Robert Broyles relating to ferritin-H as a repressor of the human β-globin gene in erythroid cells, as well as its implications in the treatment of β-globin-related diseases, such as sickle cell anemia.

They goes on to state that because the relevant target cells for this condition (adult erythroid cells) have been shown to express ferritin receptors and to take up exogenously added ferritin protein, and because other human cells (astrocytoma cells) which take up exogenous ferritin-H also transport it to the cell nucleus by an active transport mechanism, the concept of using ferritin-H or ferritin-H peptides to treat treating sickle cell anemia is a logical approach.

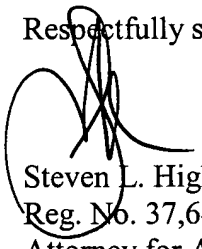
Moreover, the declarants point out that protein drugs, such as insulin and C-GSF, have been used in clinical settings for several decades. In addition, he notes, many other protein drugs have been approved by FDA in recent years. Moreover, Dr. Lin's own company, which specializes in protein drug development, has many protein drug candidates in the pipeline. Thus, it the declarants' opinion that ferritin-H is a promising candidate for treating indications such as sickle cell disease.

Thus, in sum, applicants submit that expert opinions are that use of a protein like ferritin-H as a therapeutic is not beyond the realm capabilities of the field, and further, that particular attributes of ferritin-H biology (receptor binding and nuclear translocation) make it a promising drug candidate. As such, the present enablement rejection is not well-based, and its withdrawal is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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